REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-32 are in this case. Claims 5, 6, 9, 13, 22, 23, 26 and 29 were previously withdrawn. Claims 1-4, 7, 8, 10-12, 14-21, 24, 25, 27, 28 and 30-32 were rejected. Claims 1, 7, 8, 16, 18, 19 and 21 have now been amended. Claims 2-4, 14-15, and 20 were canceled without prejudice. New claims 33-35 are added.

Priority

The Examiner has stated that the subject matter of claims 11 and 27 is not found to be supported in the applications from which the instant application claims priority. Applicant respectfully traverses these objections.

Claim 11 teaches the method of claim 1, wherein said oligosaccharide comprises at least one of DS Po912, DS 1145, DS 1020, DS 8767, DS Po821, DS 9267, DS 9517 and DS 0895.

Claim 27 teaches the method of claim 18, wherein said oligosaccharide comprises at least one of DS Po912, DS 1145, DS 1020, DS 8767, DS Po821, DS 9267, DS 9517 and DS 0895.

The instant application, at pages 21-22, provides a list of heparin and heparin sulfate disaccharides suitable for use in the method of the present invention. Po912 is taught as being Sigma H 9392; DS 1145 as Sigma H 1145; DS 1020 as Sigma H 1020; DS 8767 as Sigma H 8767; DS 9267 as Sigma H 9267; DS 9517 as Sigma H 9517; and DS 0895 as Sigma H 0895. These compounds are taught throughout the priority document, US Application No. 08/436,330, filed May 10, 1995, such as in Table XXIIIA.

With regard to DS Po821, the instant application includes an appendix of structures, which clearly shows that the structure of this novel synthetic disaccharide is that of the compound of Figure 43 of the priority document, 4-

O-(2-deoxy-6-O-sulfo-2-sulfoamino-.alpha.-D-glucopyranosyl)-(2-O-sulfo-.beta.-D-glucopyranoside) uronic acid.

Claim 1 teaches a method for treating a malignancy in a subject, hence dependent claim 11 teaches the use of the above-listed compounds for use in treatment of a malignancy. Claim 27 is dependent from claim 18, which recites a method for treating a metastatic cancer. As stated in column 7, lines 45-48, of the priority document, the substances used display a regulatory activity relating to the induction or secretion of active TNF-alpha. Furthermore, column 9, lines 51-52, states that the invention is useful in the treatment of tumors by modification of the secretion of active TNF-alpha. Table XXIIIA illustrates the results of an experiment using inhibition of swelling of the ears of mice in response to administered oxazolone, using the claimed compounds. As stated in column 46, lines 42-46, the inhibition of the T cell-mediated inflammatory response is seen as an indication that the disaccharides can down-regulate the production of active TNF-alpha. Hence, DS Po912, DS 1020, DS 9267, DS 9517 and DS 0895 were shown to be effective regulators of TNF-alpha production. The priority document at column 49, line 64, bridging column 50, line 19, provides a generic formula that embodies the structural characteristics of the regulatory compounds. This formula is identical to that provided on page 10, lines 9-20, of the instant application.

Applicant respectfully maintains that sufficient support for the priority claim is found in the applications from which the instant application claims priority.

35 U.S.C. § 112, First Paragraph Rejections

The Examiner has rejected claims 1-4, 7-8, 10-12, 14-21, 24-25, 27-28, and 30-32 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or which is most nearly connected, to practice the invention commensurate in scope with these claims.

Specifically, the Examiner has stated that the specification is enabling for treatment of specific cancers as recited in claim 15, except for colon cancers. The Examiner has further stated that the criteria defining the malignancy treatable by use of the instant method are not set forth in the specification, and that insufficient information is provided to allow the skilled artisan to ascertain these malignant disorders without undue experimentation.

In view of the Examiner's objections, claims 1 and 18 have been amended to recite the specific tumors recited in claim 15. Support is derived from original claim 15, and from the specification at page 30, last line, bridging page 31, line 8.

Claims 14 and 15 have been canceled without prejudice. Claim 16 has been amended so as to be dependent from claim 1.

The Examiner further states that heparin sulfate is taught by Timar et al. (Invasion Metastasis, 1990; 10:301-315) to enhance the growth of certain types of colon cells. Applicant respectfully disagrees. The cited document does not specify an effect on colon cells. The document teaches heparan sulfate as enhancing the growth of tumor cells of specific metastatic phenotype i.e. the 3LL cell line, but does not teach or suggest an effect of this compound on colon cells.

35 U.S.C. § 112, First Paragraph Rejections

The Examiner has rejected claims 3 and 26 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner's rejections are respectfully traversed.

Specifically, the Examiner states that the expression "oligosaccharide is heparin or heparin-sulfate derived" as recited in claim 1 renders the claim indefinite as to the compounds encompassed by the claims. Claim 1 has been amended to define the oligosaccharide as being a carboxylated or sulfated gluscosamine derivative of heparin or heparin sulfate. Support for this

amendment is derived from original claims 2 and 3, and from the specification at page 6, lines 20-23, and page 17, lines 12-13. Additional independent claims have been inserted, further defining the molecular weight and weight ranges, as supported by the specification at page 9, lines 11-14 Claims 2 and 3 have been canceled without prejudice. Claims 7 and 8 have been amended to be dependent from claim 1.

The Examiner further states that the expression "glucosamine derivative" recited in claims 3 and 19 renders the claims indefinite as to the compounds encompassed by the claims. The recitation of claim 3 has been incorporated into claim 1. Claim 3 has been canceled without prejudice. Claim 19 has been amended to teach a sulfated glucosamine derivative, as supported by original claims 4 and 20, and by the specification at page 10, lines 4-5. Claim 20 has been canceled without prejudice.

Claim 21 has been amended to be dependent from claim 19.

The Examiner further states that there is insufficient antecedent basis in claims 7 and 24 for the recitation of the limitation "in which X_1 is hydrogen... X_1 and X_2 are sulfates" in lines 3-6. Claims 7 and 24 have been amended to correct errors in the inserted formula (I), in which X_1, X_2 and X_3 were omitted. Support for this amendment is derived from the formula taught at page 10, lines 10-2- of the specification. Claim 7 is further amended to recite dependency from claim 3.

35 U.S.C. § 103(a) rejections – US Patent No. 4,822,318 in view of Vlodavsky et al. (Adv. Exp. Med. Biol., 992; 13:317-327).

The Examiner has rejected claims 1-4, 8, 10, 14-21, 25, and 30-32 under 35 U.S.C. § 103(a) as being obvious over US Patent No. 4,822,318 in view of Vlodavsky et al. (Adv. Exp. Med. Biol., 992; 13:317-327) The Examiner's rejections are respectfully traversed.

Specifically, the Examiner has stated that US Patent No. 4,882,318 teaches heparin and its related molecules for the treatment of tumor by

inhibiting heparanase activity and thereby decreasing the metastasis of the tumor, without expressly teaching the oligosaccharide compounds of the instant invention.

The Examiner further states that Vlodavsky et al. teaches that to optimize cancer therapy, one would want to chose a heparin compound that has low potential for bFGF release, but high inhibition of heparanase activity. Vlodavsky further teaches that heparanase inhibition activity and bFGF release activity are affected by size, sulfation, acetylation, and the position of sulfation or desulfation of the heparin molecules. According to the Examiner, it would therefore be obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed heparin molecules for the treatment of cancer. Applicant respectfully traverses the Examiner's objections.

Vlodavsky et al. teaches that efficient inhibition of tumor metastasis is best achieved by heparin species containing 16 sugar units or more (page 317, lines 14-15, and page 319, lines 21-22). This is contrary to the teaching of the present invention, which states (page 9, lines 14-19, and page 17, lines 6-11) that the substances of the present invention generally comprise molecules of various sugar units of which the basic unit of activity is associated with a disaccharide, but that larger oligosaccharide chains of up to about 10 sugar units can also function to inhibit metastasis. Claims 1 and 18 have been amended to include this limitation with regard to the maximum number of sugar units of the oligosaccharide. Furthermore, use of an oligosaccharide for treatment of the specific types of malignancy recited in amended claim 1 is neither taught nor suggested in the prior art documents, either alone or in combination.

The Examiner refers to Fig. 1 of Vlodavsky et al. as teaching various factors that affect heparanase inhibition activity. However, this Figure relates to release of basic fibroblast growth factor from the subendothelial extracellular matrix, which is different from inhibition of tumor metastasis (see, for example, page 317, last two lines, which state that release of bFGF and

inhibition of heparanase result in induction of neovascularization and inhibition of tumor metastasis, respectively).

It is therefore the Applicants' opinion that claims 1-3, 8, 10, 16-19, 21, 25, and 30-32 are not rendered obvious by US Patent No. 4,822,318 in view of Vlodavsky et al. (Adv. Exp. Med. Biol., 992; 13:317-327) and are therefore allowable.

In view of the above amendments and remarks it is respectfully submitted that claims 1-3, 7-8, 10-12, 16-19, 21, 24-25, 27-28, and 30-32 are now in condition for allowance. Prompt Notice of Allowance is respectfully and earnestly solicited.

D'vorah Graeser
Agent for Applicant
Registration No. 40,000

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